

Unblocking Bottlenecks: Gastrointestinal and Lung Neuroendocrine Tumors Early Detection

Valeria Giandomenico*

Dept of Medical Sciences, Endocrine Oncology, Uppsala University, Uppsala, Sweden

The main topics of my commentary are related to rare tumors active research. I therefore decided to introduce the neuroendocrine tumors at my best. I will then describe the best summary of our ongoing research, run by my group in collaboration with a pool of Swedish, European, American and Lebanese scientists in the field.

Gastrointestinal and lung neuroendocrine tumors are two independent rare malignancies, which are part of broad group of tumors called neuroendocrine tumors (NETs). They are generally characterized by an indolent course. However, some of them are lethal malignancies and their incidence is almost equivalent to mortality [1]. The complex pathophysiology, absence of early diagnostic and prognostic markers and low responsiveness to radiation and chemotherapies are major barriers against successful therapy. Poor performance of therapeutic agents, even in the initial stage of invasive cases, emphasizes the importance of early detection for improved survival. Small intestinal neuroendocrine tumor (SI-NET) belongs to the biggest group of gastroentero-pancreatic neuroendocrine tumors. They are epithelial tumors with endocrine differentiation and arise from enterochromaffin (EC) cells in the intestinal mucosa [2]. Diagnosis is delayed for up to 5 years [3,4]. As main result, the vast majority of patients are admitted to medical work-out with metastatic or inoperable disease [3,5]. Surgery is then seldom curative and conventional chemotherapy and radiotherapy are inefficient. Neuroendocrine neoplasms of the respiratory tract are managerially separated into four subgroups on the basis of clinical characteristics: typical carcinoid tumor (TC), atypical carcinoid tumor (AC), large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC) [6]. They originate from pulmonary neuroendocrine cells (PNEC). They are specialized airway epithelial, cells either solitary cells or clusters called neuroepithelial bodies in the lung. PNEC have not been clearly studied as the enterochromaffin cells [7]. Mainly TC and AC are the lung tumor types involved in our studies [8] and only radical surgery offers the best chance to survive for the patients suffering from these tumours [9].

In conclusion, the current treatments of metastasized SI-NETs and lung carcinoids aim at controlling tumor growth and hormonal secretion by using somatostatin analogues, interferon alpha; and the more recently accepted everolimus and sunitinib in clinics [1,10-12]

Early detection, which may lead to potential surgery, is crucial to cure more SI-NET and lung carcinoid patients. Indeed, it has been suggested that better NET biology understanding, improved analytical approaches to identify tumors and localizations of the small lesions and novel biomarkers detection are pivotal to improve NET patient outcomes. Several bottlenecks to NETs early detection have been addressed and they are major challenges to achieve to improve the clinical management such as, universal classification and grading system, elucidation of cell biology, development of cell lines and animal models, acquisition of genetic information, identification of serum markers for early diagnosis, definition of tissue markers to identify tumour origin, development of molecular pathological profiling to define prognosis, precise identification of topographic information (before and during surgery), identification of molecular therapeutic targets. development of improved (adjuvant) treatment for residual disease, establishment of centers of excellence and multidisciplinary speciality NET clinical teams, construction of central clinical and tissue

database resources and government focus on clinical and research funding for rare diseases [10,13]. SI- and lung-NETs symptoms are vague at the beginning and appear late at the metastatic stage most of the time. A biological marker with high sensitivity (100%) and specificity (99%) will produce high levels of false positives (up to 80%) for every positive case of cancer given the rarity of these tumors. The broad advancement in imaging made it pivotal in the staging and evaluation of NETs [14]. However, the high cost of imaging discourages the use for the follow-up of asymptomatic cases. This invites looking for highly sensitive and specific blood screening and/or tissue based strategies, also stated for different malignancies as pancreas cancer [15].

Although no methods/molecules are available to fulfill biomarker requirements for rare NETs, advanced molecular technologies, high-throughput screening strategies and individual molecules, which are differentially altered during the development of rare tumors, may be further studied to identify novel potential markers. Indeed, several studies suggested that miRNAs, protein and autoantibodies might predict tumors and response to therapy [16-21].

Our Ongoing Research to Unblock Some of Bottlenecks is Described as Follows:

Our recent findings on novel SI-NETs and lung carcinoid biomarkers [22-24] supported our research plans. First: to study of miRNAs impact and function in SI-NET as diagnostic and prognostic biomarkers in patients' blood. Second: to evaluate serum patient proteins to classify SI-NET and investigate SI-NETs auto antibodies, by using a novel immune assay. Third: to elucidate the diagnostic and thernagnostic role of the olfactory receptor 51 E1 (OR51E1) in SI-NETs and lung carcinoids [22,25,26].

SI-NET miRNAs Potential Pmpact as Diagnostic and Prognostic Biomarkers and Function

Our results on miRNA profile in patients at different stage of disease (primary tumors, mesentery metastasis and liver metastasis) [27] and those of R.V. Lloyd's group [28] addressed the role of nine microRNAs in SI-NET pathogenesis; five were up-regulated, whereas four were down regulated. MicroRNAs emerged as potential biomarkers in body fluids, mainly in serum and plasma but also in saliva [29,30]. We thus investigated and showed the nine SI-NET-specific miRNAs in blood samples, with the ultimate goal to develop mini-invasive tests to monitor tumor recurrence during the follow-up (ongoing).

*Corresponding author: Valeria Giandomenico, Associate Professor, Dept of Medical Sciences, Endocrine Oncology, Uppsala University, Uppsala, Sweden, Tel: +46(0)6111081, +46(0)702744634; Fax: +46(0)18553601; E-mail: valeria.giandomenico@medsci.uu.se

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We published miRNAs expression in SI-NET tissue [31] and we then investigated whether miRNAs expression in patient blood (serum) is similar to the one in tumor tissue. We overtook the problem of limited amount of miRNAs in blood by pre-amplifying their cDNAs as previously reported by Roth et al. [32]. We also used the Bio-Rad Digital Droplet PCR machine, which improve low expressed molecules detection in tumor tissue [33]. We collected 40 serum samples to monitor the selected miRNAs in SI-NET tissue [27]. Experiments are ongoing to complement the previous study with a new one by using blood to clarify whether to use SI-NETs blood samples is possible (Li et al., manuscript in preparation, 2013).

We also work to unveil the selected miRNA functions. We previously published that CNDT2.5 and KRJ-1, from midgut carcinoids, QGP-1, from pancreatic carcinoma, NCI-H720 and NCI-H727 from lung carcinoids express the 9 selected miRNAs [27]. We are thus using these cells as *in vitro* models to unveil whether the expressed miRNAs affects NET cells biology. We selected miR-196a as first miRNA to study by using a novel *in vitro* model. Anti-miR-196a a lentiviral-based miRNA inhibitor works as specific inhibitor to knock down miR-196a expression by using NCI-H727 cells. We showed that the transcriptional expression of Homeobox protein Hox-B7 (*HOXB7*) [34] and solute carrier family 28 (sodium-coupled nucleoside transporter), member 2 (*SLC28A2*) genes [35], is significantly up regulated when miR-196a is knocked down. Investigation the other 8 selected miRNAs is ongoing. Functional studies such as, protein expression by using Western blot analyses; and cell proliferation assays are ongoing. In conclusion, the two final goals are to develop a novel miRNA-chip, according to Bianchi et al. [36] and to unveil the 9 miRNAs functions. Hopefully, these novel findings may improve tumor biology knowledge and reduce both medical cost and patient's discomfort with a novel diagnostic and follow up tool.

Identification of Candidate Serum Proteins and Autoantibodies to Classify SI-NETs

Blood-based biomarkers are preferred over others due to blood ease of collection [15]. The lack of SI-NETs novel protein biomarkers drove our ongoing research to use two different approaches, which rely on the use of proteomics high throughput biology. We worked with a group at Science for Life Laboratory, School of Biotechnology, KTH - Royal Institute of Technology, Stockholm, Sweden, to detect candidate biomarker of SI-NET patient protein profiles. We indeed investigated proteomic signatures in serum of SI-NET patients at different stages of disease, such as primary tumor, lymph node metastasis and liver metastasis versus healthy individuals. We used a highly multiplexed antibody suspension bead array [37-39], which targeted 124 unique proteins with 184 produced antibodies and validated in the context of the Human Protein Atlas (HPA) [40] by using two different patient cohorts. To summarize our findings, we discovered sets of protein profiles, which allow discriminating SI-NET patients from healthy individuals at different stages of disease with a classification accuracy of up to 85%. We compared healthy individuals to patients suffering from primary tumors and we found that four proteins namely IGF1, IL1 α , SHKBP1, and EGR3, were significant. Similar analyses confirmed that 4 proteins, IL1 α , SHKBP1, STX2, and XIAP were significant for live node metastasis patients; whereas IGF1, IGFBP2, IL1 α , MAML3, and SHKBP1 were significant for liver metastasis patients. However, the most relevant findings suggested that IGF1, IGFBP2, IL1 α , MAML3, and SHKBP1 were able to distinguish between controls and primary tumor-bearing patients (Darmanis et al., revised version, submitted to PLOS ONE, by the end of July 2013).

The second proteomic approach used is a novel microarray immunoassay, run in collaboration with Phadia AB (Thermo Fisher Scientific), Uppsala, Sweden, to explore the potential relevance of several autoantibodies in SI-NETs at different stage of diseases. We showed that high Ma2 autoantibody titer in the blood of SI-NET patients is a sensitive and specific biomarker superior to chromogranin A (CgA) for the risk of recurrence after radical operation in 2010 [24] and this supported our interest in investigating more auto antibodies.

The ImmunoCAP ISAC platform is generally used to diagnose allergies. Indeed printed allergens on a solid phase link proteins from serum/plasma samples by incubation with labeled anti-human-antibodies [41]. We further developed the assay for tumor diagnostics, by replacing the allergens with 26 tumor-associated antigens (ENO2, Tph-1, IGF1, Notch1, Notch2, CRP, CHGA, CHGB, CTGF, TAC1, VMAT1, IA-2, CDX-2, BIRC5, CXCR4, IGF-1R, HER-2, ATP8B1, MAML3, GHS-R and IL-1 α) on the chip solid phase. Serum auto-antibodies presence was tested by utilizing anti-human antibodies labeled with fluorescent-agents. Auto-antibodies presence and the difference in quantity were measured by a randomized blinded study by using blood patient samples and healthy samples. Upon optimized conditions the assay was used to screen the presence of autoantibodies in 120 SI-NET serum samples at different stage of disease as described above. The results showed that patients express exclusively autoantibodies against nine antigens out of 26 used ones. The most relevant results are correlated to 5 different antigens; i.e. C reactive protein (CRP), enolase 2 (gamma, neuronal) (ENO2), paraneoplastic Ma antigen 2 (PNMA2), chromogranin A (CgA) and survivin (BIRC5). Moreover, autoantibody detection significantly enables SI-NET patient discrimination at different stage of disease.

In conclusion, we showed that our novel developed microarray immunoassay, which is a specific extension of the ImmunoCAP ISAC platform, offers high reliability to discriminate SI-NET patients from healthy donors and may potentially improve SI-NET patient diagnostics and follow up (Naboulsi R et al., manuscript submitted, July, 2013). Our final aim is to enlarge our studies to evaluate whether the auto antibodies can become clinical biomarkers.

OR51E1 Diagnostic and Theragnostic Impact on SI-NETs and Lung Carcinoids

Humans sense odorant thanks to the presence of one of the largest family of G protein-coupled receptors named olfactory receptor (OR) family [42,43]. ORs cover a pivotal role in the human physiology by recognizing a variety of organic molecules. Furthermore, some odorants can play either as agonist or antagonists depending on the different OR [44,45] and this shows that OR signaling transduction is highly complicated.

Some of the ORs are over expressed in different kind of tumors, such as SI-NETs and prostate cancer [22,25,26,46]. Based on previous data on the expression of olfactory receptor 51E1 (OR51E1) in lung carcinoids cell lines (NCI-H727 and NCI-720), we tested lung carcinoids. OR51E1 expression on lung carcinoids (typical and atypical) in collaboration with Prof. G. Pelosi (European Institute of Oncology, Milan, Italy) by using QRT-PCR analysis in 2009. We then performed OR51E1 immunohistochemistry analysis as previously done in SI-NETs [22] and clearly showed that OR51E1 is expressed in lung NETs. We clearly addressed the clinical relevance of OR51E1 in lung carcinoids investigating OR51E1 protein expression in 107 lung carcinoids samples (93 typical and 14 atypical). Moreover, we showed that somatostatin receptor 2, 3, and 5 protein expression compared to OR51E1 indicate

that the expression of OR51E1 is robust in the lack of SSTRs expression. Our novel findings clearly support to devise OR51E1 as alternative targets for scintigraphy for SSTs negative patients (Giandomenico, Cui et al., revised version, submitted to Modern Pathology). OR51E1, a transmembrane G protein couple receptor like the SSRs, in SI-NETs, was previously detected on SI-NET, lung carcinoids and prostate cancer by our group. We thus propose to develop novel antibody-based diagnostic and therapeutic strategies relying on the OR51E1 protein for diagnosis, follow up and therapy of rare NETs and prostate cancers.

First, we aim at developing recombinant monoclonal antibodies (mAbs) using the HuCAL technology (mAb from Serotec, AB) and test this novel OR51E1 mAbs for their capacity in modulating cell proliferation by *in vitro* analysis of both established and primary-derived cell lines. Upon expected positive results *in vivo* analysis of mAbs will be conducted availing of tumor graft models of SI-NET, lung NET and Prostate tumors. Animal models will be established by testing a pull of human cell lines such as BON1, as previously done [47-49], since the cell lines established by SI-NETs are not expressing OR51E1 (Giandomenico, Cui et al. 2013, described above) submitted to Modern Pathology). Although BON cell lines were established from neuroendocrine pancreatic tumors, they maintain cellular midgut carcinoid phenotype [47]. Moreover, the potential clinical usefulness of OR51E1 will be also explored in lung carcinoids and prostate cancer using established NCI-720 cells (lung) and LNCaP cells (prostate).

Second, focus on the uptake of radiolabeled OR51E1 in the tumor cells. The use of antibodies against tumor-associated cell surface antigens for the targeted delivery of radionuclides was introduced circa 30 years ago. One promising approach involves pre-targeted delivery of radionuclides and it has been shown to be capable of significantly increasing the radioactive uptake in tumor relative to normal organs, thereby potentially improving the efficacy of both detection and therapy of cancer. Uncoupling of the radionuclide from the tumor-targeting antibody allows the relatively slow process of antibody localization and clearance before a very rapid and highly specific delivery of the radioactive payload carried on a small molecule, such as a peptide [50]. Once established, these models will be used to test the effect of mAbs and radiolabelled mAbs on tumor proliferation as monotherapy or in combination with other radiopharmaceuticals, cytotoxic drugs, or radio sensitizers.

Third, depicting different homing and comparing uptake in tumor and healthy tissue to be able to find a suitable homing device. Indeed, when an established and efficient method of detection can detect specific uptake of the targeted substance in the tumor, this will allow replacing the radionuclide, which is suitable for detection, with an intended radionuclide for therapy. The radionuclide then releases such a high energy that it can kill tumor cells. The potential benefits expected from these research plan is that new targeted compounds will show to be useful for detecting human tumors in experimental animals and that the uptake of healthy tissue is low. This may hopefully open a window to therapeutics approaches in humans.

To unblock rare NETs early detection bottlenecks requires avoiding lack of funding and translational research to deliver promising findings to improve the clinical management. The entire group of collaborators is aware of the evaluated length of the projects and the high cost, which request safe and honest financial capital.

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¹Department of Medical Sciences, Endocrine Oncology, Uppsala University, Uppsala, Sweden

²Clinic of Endocrine Oncology, Centre of Excellence for Endocrine Tumors, Uppsala University Hospital, Uppsala, Sweden

³Science for Life Laboratory, School of Biotechnology, KTH - Royal Institute of Technology, Stockholm, Sweden

⁴Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, Sweden

⁵ Division of Pathology and Laboratory Medicine, European Institute of Oncology, Milan, Italy

⁶Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan School of Medicine, Milan, Italy

⁷Institute of Biotechnology, Uppsala University, Uppsala, Sweden

⁸Phadia AB (Thermo Fisher Scientific), Uppsala, Sweden and;

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