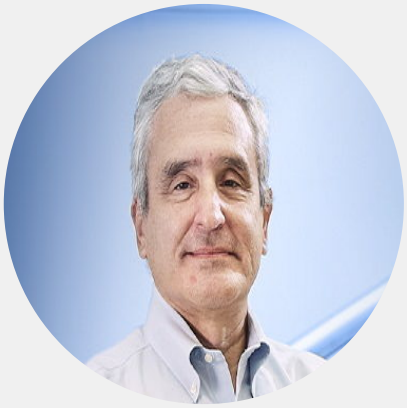
Carlo Toniatti – CSO, IRBM



It is now crystal clear that a one-size-fits-all approach is not the way to go in oncology

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Carlo Toniatti, chief scientific officer of IRBM, gives his insights into how the increased participation of early-stage ventures in the drug R&D process and the plethora of new research approaches that are recalibrating the role of CROs such as IRBM. An experienced oncologist, Toniatti also weighs in on the key emerging trends within the cancer field and assesses AI's potential as a truly transformative asset within the drug developer's toolbox.

It seems somewhat unusual for a preclinical contract research organisation (CRO) to have a chief scientific officer (CSO) position. Could you begin by explaining the importance of this role, both for a CRO itself and for its clients?

While unusual, the CSO role is a key differentiator for the company and is appreciated by our clients. At IRBM, science is our top priority, and this is assured by the presence of a CSO and the oversight they can provide. Moreover, as an oncologist by training with a long career in drug discovery and development, I like to think that I can offer expert opinions to our clients, if required. That is not to say that my role is as these companies' *de facto* CSO – they have their own excellent scientific teams – but an expert advisory role is often appreciated.

Furthermore, as a medium-sized CRO with an internal research arm, it is important for us to set clear priorities in terms of the technology platforms we focus on and the therapeutic areas in which we develop proprietary therapeutic assets. As CSO, it is my role to ensure that what we develop in-

house is done according to the highest standards and that there is no crossover or overlap with client projects.

With more and more early-stage ventures today participating in the drug R&D process, how has the role of the CRO evolved?

In the early 2000s, when I was on the “other side of the fence” at Big Pharma, we generally worked with CROs on simple chemistry projects such as the synthesis of certain scaffolds, rather than identifying and optimising molecules against novel targets or executing complex biology experiments to guide and inform the pre-clinical development of possible therapeutic agents. However, the field has completely changed, with CROs now being approached to help companies with more and more sophisticated interventions – from target identification and validation through to screening and lead identification and optimisation. In addition, as start-up companies can have less access to internal resources, they might also expect their CRO partners to develop a comprehensive drug discovery and development plan and execute with the appropriate infrastructure. This is one of our major strengths.

There is a clear outsourcing trend among Big Pharma and for this it is essential that they have reliable and consistent partners. As a spin-out of MSD, IRBM has a common heritage as experienced “drug hunters,” meaning that we closely understand Big Pharma’s needs. Specifically, we understand the culture of Big Pharma yet retain the agility of a biotech, allowing us to execute quickly. This is something many of our partners value.

Having an inter-disciplinary team of over 200 scientists, we can work collaboratively with organisations across the entire drug discovery and preclinical development phases. Within IRBM we are keenly focused on integrated pre-clinical drug discovery and with our capabilities we can support a range of organisations of various sizes, each with its own needs. As CSO, I oversee the science and the work of a team of expert scientists with a track record of success in the discovery and development of novel therapeutic agents, including small molecules, antibodies, and peptides.

The successes of smaller companies’ programs and progress to the next inflection point can be a matter of life and death. How does this play into your operations?

Our ability to identify and raise issues, and even make the science-driven suggestion to halt a program, thus saving money and time, entirely differentiates IRBM.

During the preclinical phase of drug development, moving from target identification to lead optimisation and before the execution of IND-enabling studies, there are fewer inflection points, but rather several decision points, including: establishing the appropriate screening funnel; distinguishing between “must-have” versus “nice-to-have” experiments and data; deciding which series of molecules to invest in; and defining and executing the “killer” experiments for cost- and time-effective decisions. Speed and quality are both important considerations, with some clients choosing to lean more heavily towards one or the other, although we always try to find the right balance between the two.

The industry is increasingly focused more on ‘technology platforms’ than individual drugs. The mRNA platform on which some of the COVID-19 vaccines has been based has made headlines, but is not the only approach. How does this plethora of new approaches influence IRBM’s work?

The glut of technological approaches available across the industry means that it does not make sense for a CRO like IRBM to go after all of them, although we need to stay on top of trends to ensure that we are able to give the support our clients need.

As a CRO, we need to invest in those technologies that we believe will maintain their value over time, and be ready slightly before they become “popular” within the industry. As an example, around ten years ago, proteolysis-targeting chimeras (PROTACS) and “molecular glues” were big news, so we had to be ready when they became more widely used.

In my opinion, the best way to remain at the forefront of technological innovations is to have some internal programs and not rely solely on customer-led projects. If we wait for customers, then we will receive requests for a certain novel technology when it is already too late. Through our own internal research, where we develop either drugs or a technology platform, we can be ready before a field becomes fully established and provide this expertise to our clients.

One technology that has become an increasingly hot topic is peptides, a field in which IRBM is collaborating with MSD in the fight against COVID-19. How would you characterise their potential?

Peptides are a growing field in which interest has fluctuated over the years. There was a lot of excitement around peptides in the past, but some technological limitations, including, for example,

poor pharmacokinetic profiles (i.e., short-half life in the body), and the cost of large-scale manufacturing, resulted in the commercial development of peptides with agonistic activity within a relatively narrow number of therapeutic indications.

Nowadays, the field has reached technological maturity and peptides' potential uses as therapeutic agents have hugely increased. Advancements cover the entire spectrum of peptide R&D, from the development of peptide screening platforms, such as phage display and mRNA display, to the implementation of novel chemical strategies for more rapid and cost-effective synthesis of peptides with improved potency, selectivity, and pharmacokinetic properties, as well as the optimisation of formulations for peptide delivery. Increasing oral bioavailability and cell penetration are areas where breakthroughs are still needed. Considering the great potential of peptides to inhibit protein-protein interactions more effectively than small molecules, the development of systems to efficiently deliver peptides inside cells would significantly widen the range of possible targets for peptide therapeutics, which are currently limited to extracellular targets.

Peptides are a distinct class of therapeutic agents with very unique properties. There are targets and therapeutic areas where they can outperform small molecules and antibodies. However, to develop a peptide therapeutic, it is of paramount importance to know exactly how to work with peptides and what can or cannot be achieved. Some notions and models which apply to small molecules and antibodies might not be valid for peptides. From this point of view, we are proud to leverage more than two decades of experience in this field, with a dedicated team of experts.

Given your experiences both at MSD and at the renowned MD Anderson Cancer Center, it would be remiss not to ask a question about oncology, an area that has seen a revolution in recent years driven by greater understanding and targeting of the somatic mutations that underlie cancer. What do you see as the key emerging trends in this field?

It is now crystal clear that a one-size-fits-all approach is not the way to go in oncology. Immunotherapy is providing some nice data, and PD-1 is a good example, but it does not work for all tumours. Cancer is an extremely complex set of diseases, and it is unlikely that every drug developed has the potential to make it to patients. Every cancer is different, and we will need to identify the sub-populations which respond best to certain technologies. This means that we need

to focus on the biology and modelling of cancer. The phrase used in the past was ‘from bench to bedside’, but perhaps today a better phrase is ‘bench at bedside.’

Targeted therapy is the present and will remain the future, most likely, but we also need to continue to be open-minded. Twenty years ago, identifying the genes mutated in cancer was the leading approach. This has turned out to be somewhat reductionist, but it is still true that if we identify the driver mutations in cancer, we can develop a very effective cure. After the initial wave of kinase inhibitors, then came cancer metabolism, epigenetics, DNA repair trends and so on. Today, immunotherapy is particularly interesting and will remain so, but we should avoid always “following the pack.” For instance, not everything should be about immunotherapy right now.

In the future, small molecules and antibodies will still play a critical role. Some relatively novel approaches, like protein degraders, will reach full maturity and we will also likely see more sophisticated approaches in terms of antibody engineering to enhance their functionality.

Peptides and peptide drug conjugates, which can overcome some of the current limitations of antibodies under certain conditions, will become a powerful weapon in our fight against cancer. For instance, peptides could become extremely useful to develop target-specific cancer radiotheranostics, i.e. agents that have both diagnostic and therapeutic capabilities. This is an area of growth in our industry and one that IRBM is certainly interested in.

Cell therapies, including but not limited to CAR-T and CAR-NK, have tremendous potential but a series of issues have prevented the widespread use of engineered immune cells beyond B-cell malignancies. Additional work will be required to overcome the current challenges. Cancer therapeutic vaccines and oncolytic viruses are other emerging areas with a few existing, approved agents, although the role of these therapeutic modalities for the future treatment of cancer patients has yet to be defined.

We also need to find a better way to use all our knowledge from each of these areas to develop appropriate combination therapies. This is where the oncology field is going. As a CRO, we need to ensure that we become experts in certain areas and can incorporate all of this into our integrated drug discovery programs.

Why does IRBM interact with stakeholders such as non-profits outside of its traditional client base, and where do you see the role of the CRO within the wider research ecosystem?

Working with non-profit organisations is very important to the company, and to me personally. At IRBM, one of our core values is bringing benefit to patients. While for certain diseases many companies are present and our efforts may not move the needle particularly, other diseases are very much neglected, either because of their complexity or current lack of commercial potential.

In many cases, non-profit foundations step in to fund research in these neglected areas and are looking for organisations with expertise in drug discovery. This is where we can and are very happy to help. When we work with foundations, our role is to help them to generate drugs against relevant targets and provide what they need to bring a drug into the clinic or to validate a particular approach. This type of work also helps foster technological advancement.

How do you choose the non-profit organisations with which IRBM works?

Scientists move around from academia to foundations, biotechs, and Big Pharma and often come back to us having worked together previously or having been recommended by a colleague. We like working with non-profits because they often address serious unmet clinical needs. It is a question of business but also of a real commitment to that mission. Foundations appreciate that IRBM can immediately become part of their group. Their project becomes our project, and we always commit, not only with our science but with great enthusiasm and genuine passion – driven by our desire to help patients who deserve our total commitment – and nothing less.

With companies rushing to acquire the capabilities to deal with a new paradigm in AI and data-driven drug development, is AI being oversold, especially given that we are still waiting for a global regulator to approve a drug based on AI data?

I am a big supporter of AI and feel it is going to change the drug discovery paradigm dramatically. However, this will not happen overnight; 20 years ago, some developments were predicted in the field of computer-assisted drug design, such as the potential to better understand the dynamics of protein-ligand interactions, improve ligand identification, and have screening tools available on people’s laptops. All of these things are real now, although we need to take it a couple of steps further.

I think that drug discovery AI today focuses too narrowly on chemistry, which is relatively straightforward. A new program which can “better” predict hits binding to a target is no longer an impressive feat. The current challenge is how to incorporate biology, including the

pharmacokinetics and metabolism of a drug, *in vitro* and *in vivo* toxicology data, and efficacy in appropriate models into AI. There is a need to ensure that the right data is added in the data sets, and to understand what data is relevant and what is not.

The data that is used to drive and inform AI needs to be of outstanding quality. Providing systems with the data needed to make an informed decision may not simply mean adding more data points, rather, it may be a case of adding less data but making it more relevant.

What are your hopes and aspirations for the next five years on both a company and industry level?

We want to grow in terms of size and global footprint but, with our internal research, we would also like to bring something of value to patients on our own. As Big Pharma and biotech increasingly shifts to outsourcing, we see a future where a lot of drug discovery knowledge sits within CROs. I foresee greater alliances between CROs to make their own drugs because there will be a critical mass of expertise. I strongly believe that this progress will come from greater cooperation between people and organisations with common interests and shared objectives.

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